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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,229	IBANEZ, JUAN JOSE LEGARDA	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/6/05; 9/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 17-45 are presented for examination.

Information Disclosure Statement

The Information Disclosure Statements filed May 6, 2005 and September 9, 2005 have been reviewed and considered, see the enclosed copy of PTO FORM 1449. However, with regard to reference citation Nos. 13-16, 20, 26, 43, 55, 68 and 79, only the abstracts were provided rather than the whole documentation as indicated by the Applicant. With regard to reference citation No. 77, it appears that reference pages were indicated as 1-39 is an error; it should be pages 387-399. Accordingly, these corrections were made on the PTO Form 1449 by the Examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1,3-6 and 8-13 and 28 of copending Application No. 11/111,435. The instant application and copending application are directed to same subject matter comprising treatment of alcohol dependency such as alcohol abuse with same effective daily dose with administration of same active agent (flumazenil). Instant claims differ by amounts sequentially administered and the time intervals. However, the amounts of daily dosages divided to sequentially administer to the patient and the time intervals are obvious modification since they are within the knowledge of one of ordinary skill in the art. One of ordinary skill in the art would optimize the dosing intervals and to divided known daily dosage of treating alcohol dependency according to patient's condition, severity and the factors concerning concurrent medical ragmen.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 30 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "reducing desire to drink alcohol", does not reasonably provide enablement for "**eliminating** desire to drink alcohol". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

> ***Nature of the Invention***: All of the rejected claims are drawn to a method for treating alcohol dependency comprising administering a therapeutically effective amount of flumazenil to a patient in need of such treatment wherein the flumazenil reduces or **eliminates** the desire to drink alcohol. The nature of the invention is extremely complex in that it encompasses the **actual elimination** of desire to drink alcohol (i.e. alcohol craving) such that the subject treated with above compound **totally eliminates** desire to drink alcohol.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass elimination of desire of alcohol consumption in alcohol dependency in patients, which involves a chronic illness of **undetermined etiology** with an insidious onset, showing recognizable symptoms and signs proportionate to its severity. Each of which may or may not be addressed by the administration of the claimed compound.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compound to a patient in order **to actually eliminate** alcohol desire is minimal. All of the guidance provided by the specification is directed towards **reduction** of desire rather than **total elimination** of desire of alcohol consumption.

Working Examples: All of the working examples provided by the specification are directed toward **the reduction rather than elimination** of alcohol desire.

State of the Art: While the state of the art is relatively high with regard to reduction of alcohol desire in alcohol dependency (i.e. reducing craving), the state of the art with regard to **elimination** of such condition is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **totally eliminate** development of alcohol desire in alcohol dependent subject. Currently, there is no known drug to completely antagonize the alcohol craving. The state of the art, Bjork et al. (U.S.Patent No. 5,434,156, column 1,

lines 28-35) report that drug dependency including ethanol is extremely **difficult to escape and despite** active research, there is as **yet no drugs that specifically can antagonize** the **alcohol craving** in alcohol-dependent subjects.

Predictability of the Art: The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed of physiological activity. The instant claims read on **complete elimination** of disorder with undetermined etiology. The lack of significant guidance from the specification or prior art with regard to the actual **elimination** of alcohol desire in a patient with the claimed compound makes practicing the claimed invention unpredictable in terms of **absolute or total elimination** of alcohol desire.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for **total elimination** of alcohol desire. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to elimination of cocaine desire with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the

system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding complete **elimination of alcohol desire** with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to totally **eliminate** the development of alcohol desire by administration of one of the claimed compound in alcohol dependent patient.

Therefore, a method for treating cocaine dependency comprising administering a therapeutically effective amount of flumazenil wherein flumazenil is administered to reduce or **eliminates** the desire to use alcohol is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-26, 29, 31-40, 43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record.

Gerra et al. teach ethanol addicts with dependency were treated with flumazenil in dose of **2mg/day divided into four doses** (0.5mg per dose) **IV (intravenous, parenteral) every 6 hours** (sequential) for 48 hours. (Abstract, page 63 lines 32-33). Gerra et al. teach that significant improvement in **alcohol withdrawal symptoms including tremors, sweating, nausea, depression anxiety and restlessness** shown by data when the patients were treated with flumazenil. (page 65 lines 7-10). Gerra et al. teach that some patients experienced **somnolence** during first day of the treatment with flumazenil. (page 65, first full paragraph).

Gerra et al. do not teach the specified time intervals and the specified portion of amounts set forth in claims 17, 19, 20, 24, 31, 33, 34 and 38, administering flumazenil under sedation set forth in claims 29 and 43 and administering additional agent set forth in claim 26.

Nutt et al. teach that **2mg dose** of flumazenil was administered as an **IV infusion** over **1 minute** to alcoholics in acute withdrawal. (abstract, page 338, 3rd and 4th full paragraphs). Nutt et al. teach that the other drug (additional agent) was administered after flumazenil. (page 338, 4th paragraph).

It would have been obvious to one of ordinary skill in the art to optimize the time intervals and dividing portions of known daily effective dose of flumazenil 2mg/day taught by Gerra et al. because flumazenil is effective for the treatment of symptoms of alcohol dependency in divided doses and administered in time intervals of 6 hours by Gerra et al. and Nutt et al. teach that flumazenil can also be administered over 1 minute. These references teach the extension of time intervals of flumazenil can be 1 minute to

6 hours. Accordingly, one would have been motivated to optimize the well-known effective daily dose of flumazenil for the treatment of alcohol dependency within any time intervals between 1minutes taught by Nutt et al. to 6 hour time period taught by Gerra et al. in any divided total daily dose for the treatment of alcohol dependency because as anyone of ordinary skill in the art will appreciate, preferred divided dosages and intervals are merely exemplary and serve as useful guideposts for the physician. There are, however, many reasons for varying dosages, and dosing intervals including by orders of magnitude; for instance, a patient having multiple dosing regimen or one having noncompliant would require a correspondingly dosing intervals. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. One would have been motivated to optimize the dosing intervals and optimize the daily amounts in portions to achieve an ultimate therapeutic regimen needed for individual patient's medical requirements.

With regard to administration of flumazenil under sedation set forth in claims 29 and 43, it would have been obvious to one of ordinary skill in the art to administer flumazenil, particularly while the patient is in sleep (sedation) because flumazenil causes somnolence as taught by Gerra et al. One would have been motivated to employ flumazenil while the patient is in sleep in order to take an advantage of side effect of flumazenil causing somnolence reported by Gerra et al. to achieve an additive benefit of somnolence while patient is in sleep. One would have been motivated to employ flumazenil while the patient is in sleep in order to conveniently take advantage of somnolence effect of flumazenil.

With regard to administration of additional agent after the administering flumazenil for the treatment of alcohol dependency is obvious because Nutt et al. teach that other agent (additional agent) is routinely administered after flumazenil in treatment of Nutt et al. One would have been motivated to employ additional agent for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. in order to achieve routine effect of ameliorating alcohol dependency as taught by Nutt et al.

Claims 27-28, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26, 29, 31-40, 43 and 45 above, and further in view of Opitz (U.S.Patent No. 5,519,017).

The teachings of Gerra et al. and Nutt et al. as applied as before.

Gerra et al. and Nutt et al. do not teach the specified additional agent such as clomethiazole set forth in claims 27, 41 and piracetam and disulfiram set forth in claims 28 and 42.

Optiz reports that clomethiazole, piracetam and disulfiram are the drugs used to control the influence of alcohol and the alcoholism and that clomethiazole is used for the alcoholic delirium, piracetam is used for the palliatives or the acute alcohol withdrawal and disulfiram is the most frequently used for the treatment of alcoholism. (column 1, lines 37-55).

It would have been obvious to one of ordinary skill in the art to employ other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. One would have been motivated to incorporate other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency in order to achieve at least an additive effect in treatment to alcohol dependency and achieve the expected benefit of the palliative or anti delirium effect of the each of the agent in alcohol withdrawn treatment. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) in treatment of alcoholism.

Claims 30 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26, 29, 31-40, 43 and 45 above, and further in view of Aguirre et al. (Alcohol, 1990).

The teachings of Gerra et al. and Nutt et al. as applied as before and additional teaching of Gerra et al. as follows.

Gerra et al. teach that there is observation of significant rise in plasma concentrations of beta-endorphin after administration of flumazenil. (page 65, lines32-25).

Gerra et al. and Nutt et al. do not teach the reduction or elimination of the desire to drink alcohol by flumazenil.

Aguirre et al. teach that the decrease level of beta-endorphin is a cause chronic consumption of alcohol in alcoholism. (abstract).

It would have been obvious to one of ordinary skill in the art that the employment of flumazenil for the treatment of alcohol dependency as modified by Nutt et al. would result in the reduction in alcohol consumption because Gerra et al. teach that flumazenil significantly raise the plasma concentration of beta-endorphin and Aguirre et al. teach that decreased level of beta-endorphin caused alcohol consumption. One would have been motivated to employ flumazenil as taught by Gerra et al. as modified by Nutt et al. for the treatment of alcohol dependency to reduce the alcohol consumption in order to achieve an expected benefit of flumazenil's effectiveness in eliminating the cause of alcohol consumption by increasing beta-endorphin level in alcoholics.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 5:30 am to 2 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer Kim
Patent Examiner
Art Unit 1617

Jmk
April 11, 2006